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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 401/04, 471/04, 487/04
A61K 31/47, 31/44

A1

(11) International Publication Number: WO 93/25545

(43) International Publication Date: 23 December 1993 (23.12.93)

(21) International Application Number: PCT/KR93/00044

(22) International Filing Date: 19 May 1993 (19.05.93)

(30) Priority data:
1992-9929 9 June 1992 (09.06.92) KR

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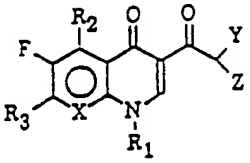
(81) Designated States: AU, BR, CA, FI, HU, RU.

Published
With international search report.

(54) Title: NOVEL QUINOLINE DERIVATIVES AND PROCESSES FOR PREPARING THE SAME



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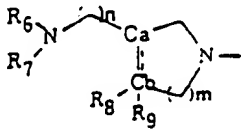

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(57) Abstract

The present invention relates to novel quinoline derivatives of formula (I) wherein, R_1 is a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms, a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms which is substituted with a halogen atom, a phenyl group or a phenyl group substituted with one or two halogen atoms; R_2 is a hydrogen atom, a lower alkyl or amino group; R_3 is a halogen atom or a substituted or unsubstituted heterocyclic group represented by formula (A) which contains at least one nitrogen atom as a hetero atom in the ring, wherein R_6, R_7, R_8 and R_9 are each hydrogen atoms or lower alkyl groups, or two of these groups may form a bond, m and n are 0 or 1, and C_a-C_b may not form a bond, or is single or double bond; X is nitrogen atom or C-R_4 wherein R_4 is hydrogen or halogen atom, or lower alkyl or lower alkoxy group; and Y and Z are each hydrogen atoms, or electron withdrawing groups, for example, ester, cyano, nitro, acyl or substituted acyl, substituted or unsubstituted amide, lower alkylsulfoxy or lower alkylsulfonyl group, and pharmaceutically acceptable acid addition salts thereof, and also to processes for preparing these compounds. The present invention also provides an antibacterial composition comprising a compound of formula (I) or its acid addition salt as an active ingredient and pharmaceutically acceptable excipients. The novel quinoline derivatives of the present invention have an excellent antibacterial activity against bacteria or bacteroides.

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NOVEL QUINOLINE DERIVATIVES AND PROCESSES FOR PREPARING THE SAME

Field of the Invention

The present invention relates to novel quinoline derivatives and pharmaceutically acceptable acid addition salts thereof which possess a broad spectrum of potent antibacterial activities and are useful as human or veterinary medicaments, and to processes for preparing such compounds.

The present invention also relates to antibacterial compositions containing one or more these compounds as active ingredients.

Description of the Prior Art

A number of quinolone compounds having a pyridone carboxylic acid as a basic skeleton have been developed, and these compounds have mainly been developed to have a potent and broad spectrum of antibacterial activities.

Among these quinolone derivatives, norfloxacin (Japanese Patent Application Laid-Open No. 141286/1978), enoxacin (Japanese Patent Application Laid-Open No. 310421/1980), ofloxacin (Japanese Patent Application Laid-Open No. 469861/1982), ciprofloxacin (Japanese Patent Application Laid-Open No. 76667/1983) and the like have been on the market. Tosufloxacin and the like recently has become commercially available.

All of these prior art compounds have a carboxy group at the C-3 position of the quinolone nucleus and this type of quinolone antibacterial compounds are crowded in the art. Thus, the development of another type of quinolone antibacterial compounds having a different skeleton is still needed.

Summary of the Invention

Based on the fact that a carboxylic acid can ionize, the present inventors have introduced the electron withdrawing groups into the α-position of a carbonyl group at

the C-3 position in order to give an acidic proton at the α-position of a carbonyl group.

As a result, it has been surprisingly found that new compounds of the present invention have improved antibacterial activities over the prior art compounds.

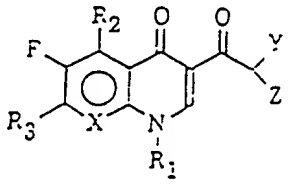
Accordingly, the present invention is concerned with novel quinoline derivatives and their pharmaceutically acceptable acid addition salts, antibacterial compositions containing such compounds, and with processes for preparing such compounds.

Detailed Description of the Invention

An object of the present invention is to provide novel quinoline derivatives and their pharmaceutically acceptable acid addition salts having an excellent antibacterial activity and also to provide processes for preparing these compounds.

Another object of the present invention is to provide antibacterial compositions containing one or more these compounds as active ingredients.

The present invention provides novel quinoline derivatives represented by the formula (I)



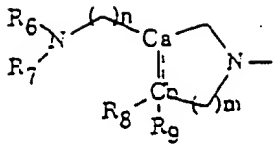
(I)

wherein:

R_1 is a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms, a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms which is substituted with a halogen atom, a phenyl group or a phenyl group substituted with one or two halogen atoms;

R_2 is a hydrogen atom, a lower alkyl or amino group;

R_3 is a halogen atom or a substituted or unsubstituted heterocyclic group represented by the following formula (A) which contains at least one nitrogen atom as a hetero atom in the ring;



(A)

wherein:

R_6, R_7, R_8 and R_9 are each hydrogen atoms or lower alkyl groups, or two of these groups may form a bond, m and n are 0 or 1, and C_a-C_b may not form a bond, or is a single or double bond;

X is nitrogen atom or C-R_4 wherein R_4 is hydrogen or halogen atom, or lower alkyl or lower alkoxy group; and

Y and Z are each hydrogen atoms, or electron withdrawing groups, for example, ester, cyano, nitro, acyl or substituted acyl, substituted or unsubstituted amide, lower alkylsulfoxy or lower alkylsulfonyl group, and pharmaceutically acceptable acid addition salts thereof.

The present invention also provides an antibacterial compositions which contain compounds represented by the formula (I) as active ingredients.

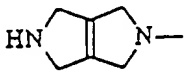
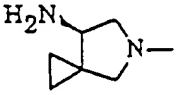
The present invention is further illustrated hereinbelow.

The novel quinoline derivatives of the present invention can be represented by the formula (I) above. These compounds exhibit an excellent antibacterial activity, particularly against bacteria or bacteroides. Therefore, the compounds of the present invention are useful in the prophylaxis and therapy for local or systemic infection caused by the above pathogens.

The present invention also includes pharmaceutically acceptable acid addition salts of the compounds represented by the above formula (I).

Pharmaceutically acceptable salts include inorganic salts such as hydrochloride, sulfate, nitrate and the like, and organic salts such as lactate, ascorbate, maleate, malonate, glutamate, citrate, fumarate, p-toluate, succinate, methanesulfonate and the

like.

Preferred compounds of the present invention are those wherein R_1 is an ethyl, cyclopropyl, 2-fluoroethyl or 2,4-difluorophenyl group, and R_3 is a substituted or unsubstituted piperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, 3-aminomethyl-2,5-dihydropyrrole,  or  group.

The typical representatives of the compounds represented by the above formula (I) according to the present invention are as follows:

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline trifluoroacetate;

1-cyclopropyl-6,8-difluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-(2,4-difluorophenyl)-6-fluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxo-1,8-naphthyridine hydrochloride;

1-(2,4-difluorophenyl)-6-fluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-5-amino-6,8-difluoro-7-(3,5-cis-dimethylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-ethyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-(2-fluoroethyl)-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(7-amino-5-azaspiro[2.4]hept-5-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-acetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-trifluoroacetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-dicyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diacetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methyl-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-5-methyl-6-fluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

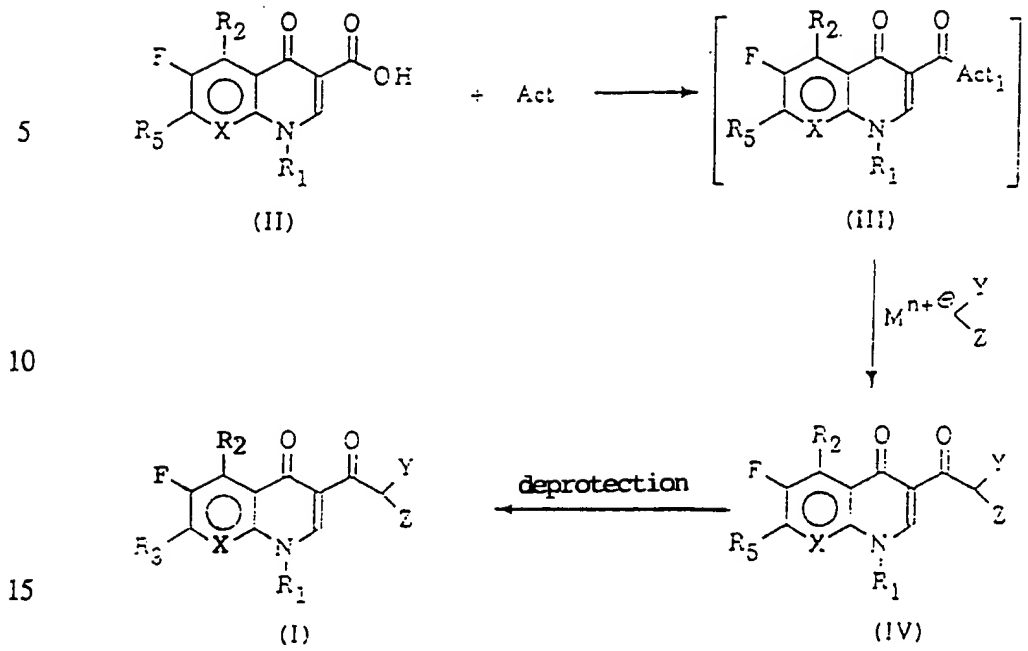
1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-amido-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride; and

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminomethylpyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride.

The quinoline derivatives according to the present invention may be prepared by the processes illustrated hereinbelow.

In these reaction schemes, the abbreviations, Act, Act_1, M^{n+}, Et, Me and Ac mean a carboxylic acid activating reagent, an carboxyl activating group, and alkali or alkaline earth metal ion, ethyl, methyl and acetyl, respectively, and R_1, R_2, X, Y and Z are the same as defined in the above formula (I). R_5 means R_3 having protected amino group, and R means a lower alkyl group such as CH_3 or a lower haloalkyl group such as CF_3.

The compound of formula (I) according to the present invention may be prepared as follows: A carboxy group of the quinoline compound represented by the following formula (II) is activated with a carboxylic acid activating reagent to give a compound of the following formula (III), the compound (III) thus obtained is then reacted with an alkali or alkaline earth metal salt of a compound having an activated methylene group represented by the formula, $Y\text{-}CH_2\text{-}Z$ to give a compound of the following formula (IV), and finally the deprotection of the compound (IV) is carried out to give the above compound (I). This reaction scheme may be illustrated as follows:



In the above reaction scheme, Act is a carboxy group activating reagent for facilitating the coupling reaction by activating the carboxy group. These activating reagent may be selected from the group consisting of carbonyl diimidazoles, alkoxychloroformates, organic acid anhydrides, carbonates and phosphonates.

Act_1 is a carboxyl activating group. The activating group may be -CN, a substituted or unsubstituted phenoxy group, an imidazole group, an activated carbonate group. an activated ester group of organic acid, or a mixed anhydride and the like.

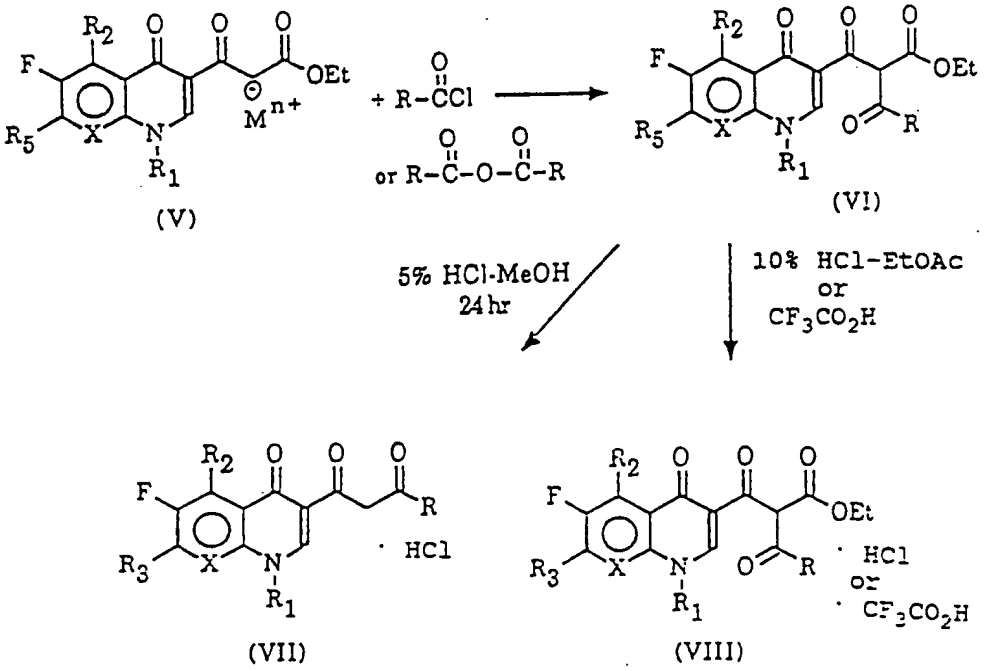
M^{n+} is alkali or alkaline earth metal ions such as Na^+, K^+ or Mg^{2+}.

The deprotection reaction is preferably carried out in a 1-10% HCl-methanol solution, CF_3CO_2H or a 1-10% HCl-ethylacetate solution at a temperature between about 0° and about 80°C.

An alternate process for preparing compounds of formula (I) according to the present invention may be carried out by reversing the role as a nucleophile of a starting

material of the above reaction with the reactants (Y-CH_2-Z) when the reactivity of these reactants in the substitution reaction is low due to their weak nucleophilicity.

That is, in case of Y-CH_2-Z compound having an activated methylene group with the weak reactivity, the compound of the following formula (V) is reacted with an acylhalide or an organic acid anhydride to give a compound of the following formula (VI), and then the deprotection reaction of the compound (VI) is carried out to give the following compound (VII) or (VIII). The above reaction may be illustrated hereinbelow.

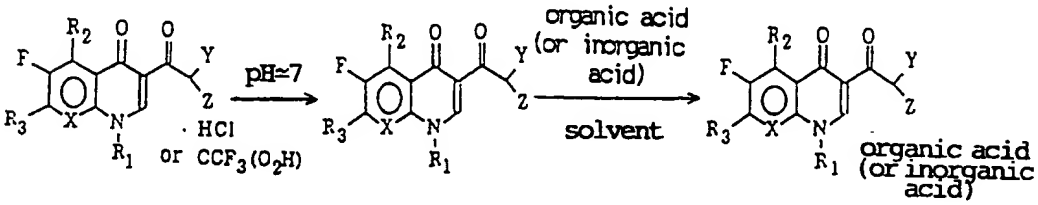


In the above reaction scheme, compound (V) is prepared from compound (II).

Furthermore, organic acid or inorganic acid salts of compound (I) may be prepared as follows: The salt of the compound (I) synthesized in accordance with the above reaction, for example, its hydrochloride or trifluoroacetate is dissolved in water and the pH of the solution is adjusted to about 7. The resulting solid (base compound) is filtered and then dried. The dried solid is dissolved in a lower alkanol such as methanol or ethanol or a haloalkane such as chloroform, dichloromethane or 1,2-dichloroethane or a mixture thereof, and then an equivalent amount of the

corresponding acid is added to the mixture to give an acid addition salt of the compound (I). Acids used in the present invention include organic acids such as lactic acid, ascorbic acid, maleic acid, malonic acid, glutamic acid, citric acid, fumaric acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, propionic acid, tartaric acid, succinic acid, methanesulfonic acid and the like; and inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid and the like. All these pharmaceutically acceptable salts are also embraced within the scope of the present invention.

A process for preparing these acid addition salts may be illustrated hereinbelow.



The compounds according to the present invention are effective particularly against bacteria and bacteroides, and thus useful for the prophylaxis and therapy against a local or systemic infection caused by these pathogens in humans and other animals.

The compounds of the present invention may be administered topically, orally, parenterally or rectally. Among these administrations, a parenteral administration such as an intravenous or intramuscular, or an oral administration is preferred.

In general, it is advantageous to administer the compounds of the present invention in the amount of about 0.1 to about 500mg/kg, preferably about 0.5 to about 100mg/kg of body weight per day optionally in divided doses for human or veterinary use. It is advantageous to administer the compounds of the present invention in the amount of about 0.1 to about 200mg/kg, preferably about 0.3 to about 50mg/kg of body weight in one single dose. However, it should be understood that the amount of the compound actually administered may be varied beyond the above range of dosages depending on the weight and response of an individual patient, the severity of the patient's symptom, the form of formulation, the chosen route of administration, the number of times or interval of administration and the like. At this time, the optimum dosage and the administration route of the active compound may be determined by those skilled in the art.

One or more compounds of the present invention may be either administered as such, or formulated for administration by mixing therewith non-toxic, inert pharmaco-dynamically acceptable excipients. The present invention also includes these compounds and pharmaceutical preparations, and processes for preparing them.

Examples of such non-toxic, inert pharmacodynamically acceptable excipients are solid, semi-solid or liquid diluents, fillers and auxiliaries.

Preferred pharmaceutical formulations are tablet, sugar-coated tablet, capsule, granule, suppository, solution, suspension, emulsion, paste, ointment, cream, lotion, powder, spray and the like.

In case of tablet, sugar-coated tablet, capsule and granule, the active compound of the present invention may be combined with conventional excipients, e.g., fillers and extenders such as starch, lactose, sucrose, glucose, mannitol and the like; binders such as carboxymethyl cellulose, alginate, gelatine, polyvinylpyrrolidone and the like; disintegrants such as calcium carbonate, sodium bicarbonate and the like; solution retardants such as paraffin; absorption accelerants such as quarternary ammonium compound and the like; wetting agents such as cetyl alcohol, glycerin monostearate and the like; adsorbents such as kaoline, bentonite and the like; lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycol and the like; or mixtures thereof.

The tablet, sugar-coated tablet, capsule, pill, granule and the like may be coated with conventional coating materials including any opacifier.

The suppository may contain conventional aqueous or nonaqueous excipients, e.g., polyethylene glycol, fat, high molecular ester or mixtures thereof in addition to the active compounds.

The ointment, paste, cream, gel and the like may contain conventional excipients, e.g., animal or vegetable fat, wax, paraffin, starch, cellulose derivatives, polyethylene glycol, bentonite, talc, zinc oxide or mixtures thereof in addition to the active compounds.

The solution or emulsion may contain conventional excipients such as solvent, solubilizer and emulsifier, e.g., water, ethyl alcohol, benzyl benzoate, propylene glycol; oils such as cotton seed oil, peanut oil, corn seed oil or olive oil; fatty acid esters of glycerin, polyethylene glycol or sorbitan, or mixtures thereof in addition to the active compounds.

The solution or emulsion for parenteral administration may contain a sterilized isometric solution or emulsion.

The suspension may contain conventional excipients, e.g., liquid diluents such as water, ethyl alcohol, propylene glycol, or suspending agent.

The above formulations may further contain dyes, preservatives, fragrants, sweeteners and additives.

The formulations may comprise about 0.1 to about 99.5% by weight, preferably about 0.5 to about 95% by weight of the therapeutically active compounds of the present invention.

It will be readily apparent to those skilled in the art that certain changes and modifications may be made to this invention without departing from the spirit or scope of the invention.

The following examples are given to illustrate this invention without limiting them in any way.

Example 1: Preparation of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

3.31g of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was dissolved in a mixture of 30ml of methanol and 20ml of chloroform, and the resulting solution was stirred at 50°C for 5 hours after addition of 2.29g of di-t-butylcarbonate thereto. The solvent was removed under reduced pressure to obtain 4.2g of the object compound (yield: 97%).

Elementary analysis for $C_{22}H_{26}FN_3O_5$

	C(%)	H(%)	N(%)
Calculated	61.24	6.07	9.74
Found	62.17	6.13	9.51

Example 2: Preparation of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboimidazolide

4.31g of the compound obtained from Example 1 was dissolved in 50ml of chloroform, and 1.9g of carbonylimidazole was added thereto. The resulting mixture was refluxed for 4 hours, and then the solvent was distilled off under reduced pressure to obtain the object compound. This object compound was used without further purification in the following Example.

Example 3: Preparation of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline

To the compound obtained from Example 2 were added 100ml of tetrahydrofuran, and then 1.4g of potassium t-butoxide and 3.05g of nitromethane in turn. The resulting mixture was refluxed for overnight. The reaction mixture was cooled to room temperature and its pH was adjusted to about 3.3 with 2N HCl. The mixture was extracted three times with 300ml of ethylacetate, and then purified on a silica gel column chromatography to isolate 4.03g of the object compound (yield: 85%).

Elementary analysis for $C_{22}H_{27}FN_4O_6$

	C(%)	H(%)	N(%)
Calculated	58.22	5.74	11.81
Found	58.10	5.79	11.71

Example 4: Preparation of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

(Process 1)

4.7g of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline obtained from Example 3 was dissolved in 50ml of 5% HCl-methanol solution and then stirred at room temperature for 5 hours.

The solvent was distilled off under reduced pressure, and the solid formed after addition of 50ml of acetone was filtered to obtain 2.96g of the above object compound (yield: 72%).

Elementary analysis for $C_{18}H_{20}ClFN_4O_4$

	C(%)	H(%)	N(%)
Calculated	52.62	4.91	13.64
Found	52.55	4.99	13.53

(Process 2)

4.7g of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline obtained from Example 3 was dissolved in 50ml of 10% HCl-ethylacetate solution, and the resulting solid was filtered and then dried to obtain 3.78g of the above object compound (yield: 92%).

Elementary analysis for $C_{18}H_{20}ClFN_4O_4$

	C(%)	H(%)	N(%)
Calculated	52.62	4.91	13.64
Found	52.55	4.99	13.53

Example 5: Preparation of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline trifluoroacetate

4.7g of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline obtained from Example 3 was dissolved in 20ml of trifluoroacetic acid and then stirred for 10 minutes. The solvent was removed, and the solid formed after addition of 50ml of acetone was filtered and then dried to obtain 4.25g of the object compound (yield: 87%).

Elementary analysis for $C_{20}H_{20}F_4N_4C_6$

	C(%)	H(%)	N(%)
Calculated	49.19	4.13	11.47
Found	49.03	4.19	11.35

Example 6: Preparation of 1-cyclopropyl-6,8-difluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.5g of 1-cyclopropyl-6,8-difluoro-7-(piperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 2.6g of the object compound (yield: 62%).

Elementary analysis for $C_{18}H_{19}ClF_2N_4O_4$

	C(%)	H(%)	N(%)
Calculated	50.42	4.47	13.07
Found	50.33	4.51	12.99

Example 7: Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.6g of 1-cyclopropyl-6,8-difluoro-7-(3-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 1.82g of the object compound (yield: 41%).

Elementary analysis for $C_{19}H_{21}ClF_2N_4O_4$

	C(%)	H(%)	N(%)
Calculated	51.53	4.78	12.65
Found	51.67	4.81	12.80

Example 8: Preparation of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxo-1,8-naphthyridinehydrochloride

4.0g of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 2.47g of the object compound (yield: 51%).

Elementary analysis for $C_{20}H_{17}ClF_3N_5O_4$

	C(%)	H(%)	N(%)
Calculated	49.65	3.54	14.47
Found	49.58	3.59	14.39

Example 9: Preparation of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.0g of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 2.12g of the object compound (yield: 44%).

Elementary analysis for $C_{21}H_{18}ClF_3N_4O_4$

	C(%)	H(%)	N(%)
Calculated	52.24	3.76	11.60

Found	52.21	3.80	11.65

Example 10: Preparation of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.2g of 1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 1.54g of the object compound (yield: 31%).

Elementary analysis for $C_{22}H_{20}ClF_3N_4O_4$

	C(%)	H(%)	N(%)
Calculated	53.18	4.06	11.28
Found	53.30	4.11	11.21

Example 11: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 2.18g of the object compound (yield: 49%).

Elementary analysis for $C_{18}H_{19}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	48.55	4.30	12.58
Found	48.49	4.40	12.51

Example 12: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-amino-pyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 2.0g of the object compound (yield: 45%).

Elementary analysis for $C_{18}H_{19}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	48.55	4.30	12.58
Found	48.41	4.38	12.55

Example 13: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-amino-pyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 2.45g of the object compound (yield: 55%).

Elementary analysis for $C_{18}H_{19}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	48.55	4.30	12.58
Found	48.46	4.35	12.49

Example 14: Preparation of 1-cyclopropyl-5-amino-6,8-difluoro-7-(3,5-cis-dimethylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.9g of 1-cyclopropyl-5-amino-6,8-difluoro-7-(3,5-cis-dimethylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 1.18g of the object

compound (yield: 25%).

Elementary analysis for $C_{20}H_{24}ClF_2N_5O_4$

	C(%)	H(%)	N(%)
Calculated	50.91	5.13	14.84
Found	51.01	5.15	14.90

Example 15: Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.8g of 1-cyclopropyl-6,8-difluoro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 1.68g of the object compound (yield: 37%).

Elementary analysis for $C_{20}H_{21}ClF_2N_4O_4$

	C(%)	H(%)	N(%)
Calculated	52.81	4.65	12.32
Found	52.77	4.68	12.30

Example 16: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 1.36g of the object compound (yield: 29%).

Elementary analysis for $C_{20}H_{21}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	50.97	4.49	11.89
Found	51.05	4.51	11.83

Example 17: Preparation of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline

4.3g of 1-cyclopropyl-6-fluoro-7-(4-t-butoxycarbonylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid obtained from Example 1 was dissolved in 100ml of dichloromethane, and then 1.03ml of ethylchloroformate was added thereto. The reaction mixture was cooled to 0°C, and then 1.46ml of triethylamine was slowly added thereto. Magnesium salt of diethylmalonate formed from 1.17g of $Mg(OEt)_2$ and 1.6g of diethylmalonate was dissolved in 30ml of diethyl ether, and this solution was slowly added dropwise to the above reaction solution. The reaction mixture was stirred at room temperature for 5 hours. The pH of the reaction mixture was adjusted to about 3 with 1N-HCl, and the mixture was extracted three times with 500ml of ethylacetate.

The reaction mixture was dehydrated with anhydrous magnesium sulfate ($MgSO_4$), and then the solvent was distilled off under vacuum. The residue was purified on a silica gel column chromatography to obtain 3.67g of the object compound (yield: 64%).

Elementary analysis for $C_{29}H_{36}FN_3O_8$

	C(%)	H(%)	N(%)
Calculated	60.72	6.33	7.33
Found	60.66	6.41	7.25

Example 18: Preparation of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.74g of the compound obtained from Example 17 was dissolved in 100ml of 10%

HCl-ethylacetate solution, and the solution was stirred for 2 hours. The resulting solid was filtered, and then dried to obtain 4.95g of the object compound (yield: 97%).

Elementary analysis for $C_{24}H_{29}ClFN_3O_6$

	C(%)	H(%)	N(%)
Calculated	56.53	5.73	8.24
Found	56.55	5.74	8.21

Example 19: Preparation of 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.74g of the compound obtained from Example 17 was dissolved in 200ml of 5% HCl-methanol solution, and then 0.5ml of distilled water was added thereto. This solution was stirred at room temperature for 24 hours. The solvent was distilled off and concentrated under reduced pressure. 20ml of acetone and 100ml of diethyl ether were added thereto, and the resulting solid was filtered and then dried to obtain 2.71g of the object compound (yield: 62%).

Elementary analysis for $C_{21}H_{25}ClFN_3O_4$

	C(%)	H(%)	N(%)
Calculated	57.60	5.75	9.60
Found	57.57	5.84	9.50

Example 20: Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.5g of 1-cyclopropyl-6,8-difluoro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 17 and 18 to obtain 2.69g of the object compound (yield: 51%).

Elementary analysis for $C_{24}H_{28}ClF_2N_3O_6$

	C(%)	H(%)	N(%)
Calculated	54.60	5.35	7.96
Found	54.59	5.36	7.95

Example 21: Preparation of 1-cyclopropyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.5g of 1-cyclopropyl-6,8-difluoro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 17 and 19 to obtain 1.46g of the object compound (yield: 32%).

Elementary analysis for $C_{21}H_{24}ClF_2N_3O_4$

	C(%)	H(%)	N(%)
Calculated	55.33	5.31	9.22
Found	55.21	5.39	9.18

Example 22: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 3.1g of the object compound (yield: 57%).

Elementary analysis for $C_{24}H_{28}Cl_2FN_3O_6$

	C(%)	H(%)	N(%)

Calculated	52.95	5.18	7.72
Found	52.99	5.20	7.71

Example 23: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-amino-pyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 3.32g of the object compound (yield: 61%).

Elementary analysis for $C_{24}H_{28}Cl_2FN_3O_6$

	C(%)	H(%)	N(%)
Calculated	52.95	5.18	7.72
Found	52.83	5.22	7.70

Example 24: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-amino-pyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 2.99g of the object compound (yield: 55%).

Elementary analysis for $C_{24}H_{28}Cl_2FN_3O_6$

	C(%)	H(%)	N(%)
Calculated	52.95	5.18	7.72
Found	53.00	5.20	7.71

Example 25: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 21 to obtain 1.08g of the object compound (yield: 23%).

Elementary analysis for $C_{21}H_{24}Cl_2FN_3O_4$

	C(%)	H(%)	N(%)
Calculated	53.40	5.12	8.90
Found	53.34	5.17	8.88

Example 26: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-amino-pyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 21 to obtain 1.42g of the object compound (yield: 30%).

Elementary analysis for $C_{21}H_{24}Cl_2FN_3O_4$

	C(%)	H(%)	N(%)
Calculated	53.40	5.12	8.90
Found	53.48	5.15	8.89

Example 27: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-amino-pyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 21 to obtain 1.32g of the object compound (yield: 28%).

Elementary analysis for $C_{21}H_{24}Cl_2FN_3O_4$

	C(%)	H(%)	N(%)
Calculated	53.40	5.12	8.90
Found	53.31	5.17	8.88

Example 28: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylamino-methyl-2,5-dihydropyrrol-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-(N-methyl-t-butoxycarbonylamino)-methyl-2,5-dihydropyrrol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 3.59g of the object compound (yield: 63%).

Elementary analysis for $C_{26}H_{30}Cl_2FN_3O_6$

	C(%)	H(%)	N(%)
Calculated	54.74	5.30	7.37
Found	54.77	5.31	7.38

Example 29: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylamino-methyl-2,5-dihydropyrrol-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-(N-methyl-t-butoxycarbonylamino)-methyl-2,5-dihydropyrrol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a

starting material was subjected to the same process as described in Example 21 to obtain 1.34g of the object compound (yield: 27%).

Elementary analysis for $C_{23}H_{26}Cl_2FN_3O_4$

	C(%)	H(%)	N(%)
Calculated	55.43	5.26	8.43
Found	55.35	5.30	8.40

Example 30: Preparation of 1-ethyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.4g of 1-ethyl-6,8-difluoro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 9 to obtain 2.25g of the object compound (yield: 54%).

Elementary analysis for $C_{17}H_{19}ClF_2N_4O_4$

	C(%)	H(%)	N(%)
Calculated	48.99	4.59	13.44
Found	49.02	4.61	13.38

Example 31: Preparation of 1-(2-fluoroethyl)-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.6g of 1-(2-fluoroethyl)-6,8-difluoro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 9 to obtain 1.96g of the object compound (yield: 45%).

Elementary analysis for $C_{17}H_{18}ClF_3N_4O_4$

	C(%)	H(%)	N(%)
Calculated	46.96	4.17	12.89
Found	47.01	4.18	12.87

Example 32: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonyl-aminopyrrolidin-1-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was dissolved in 20ml of ethyleneglycol dimethylether, and 1.94g of carbonyl diimidazole was added thereto. The resulting reaction mixture was refluxed for 4 hours. 1.97g of dimethylsulfone and 0.84g of 60% sodium hydride were stirred in 20ml of a mixture (1:2) of dimethylsulfoxide and ethyleneglycol dimethylether at 60°C for 1 hour to obtain sodium dimethylsulfonate. Sodium dimethylsulfonate thus obtained was added to the above reaction mixture, and then reacted at 60°C for 2 hours. The reaction mixture was acidified with 2ml of anhydrous acetic acid, extracted three times with 300ml of ethylacetate, and then dehydrated with $MgSO_4$. The solvent was distilled off under reduced pressure. The residue was purified on a silica gel column chromatography to obtain 3.58g of the object compound (yield: 66%).

Elementary analysis for $C_{24}H_{29}ClFN_3O_6S$

	C(%)	H(%)	N(%)
Calculated	53.18	5.39	7.75
Found	53.09	5.44	7.71

Example 33: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.4g of the compound obtained from Example 32 was dissolved in 10% HCl-ethylacetate solution, and then stirred for 30 minutes. The resulting solid was filtered,

and then dried to obtain 4.49g of the object compound (yield: 94%).

Elementary analysis for $C_{19}H_{22}Cl_2FN_3O_4S$

	C(%)	H(%)	N(%)
Calculated	47.71	4.64	8.78
Found	47.73	4.64	8.77

Example 34: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo-[3.3.0]oct-1,5-en-3-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 2.2g of the object compound (yield: 47%).

Elementary analysis for $C_{20}H_{19}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	51.19	4.08	11.94
Found	51.27	4.11	11.91

Example 35: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(7-amino-5-azaspiro[2.4]hept-5-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(7-t-butoxycarbonylamino-5-azaspiro[2.4]hept-5-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 1.93g of the object compound (yield: 41%).

Elementary analysis for $C_{20}H_{21}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	50.97	4.49	11.89
Found	50.95	4.52	11.85

Example 36: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo-[3.3.0]oct-1,5-en-3-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1, 17 and 18 to obtain 1.42g of the object compound (yield: 25%).

Elementary analysis for $C_{26}H_{28}Cl_2FN_3O_6$

	C(%)	H(%)	N(%)
Calculated	54.94	4.97	7.39
Found	54.98	4.99	7.38

Example 37: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-acetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride obtained from Example 25 was dissolved in 100ml of MeOH, and then 3ml of Et_3N was added thereto. 2.18g of di-t-butyldicarbonate was added to the above reaction mixture, and then stirred at 50°C for 2 hours. The solvent was distilled off under reduced pressure. Water and ethylacetate were added to the residue. The pH of the reaction mixture was adjusted to about 5 with 1N HCl, and then the organic layer was separated. The organic layer thus separated was dehydrated with anhydrous $MgSO_4$, and then the solvent was removed to obtain 5.09g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylpyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline (yield: 95%).

The compound thus obtained was dissolved in 50ml of toluene, and 1.2g of $Mg(OEt)_2$ was added thereto. The reaction mixture was acetylated with 0.74ml of acetyl chloride. The reaction mixture was stirred at room temperature for 3 hours, and 100ml of water was added thereto. The pH of the reaction mixture was adjusted to about 3 with 1N HCl, and then extracted three times with 300ml of ethyl acetate. The organic layer was separated, and then dehydrated with anhydrous $MgSO_4$. The solvent was distilled off under reduced pressure, and then the residue was separated on silica gel. The solvent was removed, and 100ml of 5% HCl-MeOH solution was added thereto. The reaction mixture was stirred at 25°C for 24 hours, and then the solvent was distilled off under reduced pressure at low temperature. A little amount of mixture (3:1) of ethyl ether and acetone was added to the above concentrated reaction mixture, and the resulting solid was filtered, and then dried to obtain 1.17g of the object compound (yield: 28%).

Elementary analysis for $C_{20}H_{22}Cl_2FN_3O_3$

	C(%)	H(%)	N(%)
Calculated	54.31	5.01	9.50
Found	54.26	5.10	9.47

Example 38: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-trifluoroacetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.7g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride obtained from Example 25 and 2.1g of trifluoroacetic acid anhydride as starting materials were subjected to the same process as described in Example 37 to obtain 0.89g of the object compound (yield: 18%).

Elementary analysis for $C_{20}H_{19}Cl_2F_4N_3O_3$

	C(%)	H(%)	N(%)

Calculated	48.40	3.86	8.47
Found	48.46	3.88	8.45

Example 39: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.2g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid imidazolide and 6.9g of potassium carbonate were put into 200ml of acetonitrile, and 5.66g of ethyl cyanoacetate was added thereto, and then refluxed under heating for 5 hours. Acetonitrile was distilled off under reduced pressure, and then water and ethyl acetate were added thereto. The pH of the reaction mixture was adjusted to about 3 with 1N-HCl, and then the organic layer was separated. The organic layer was dehydrated with anhydrous $MgSO_4$, and the solvent was distilled off under reduced pressure. The residue was purified on a silica gel column chromatography, and 50ml of 10% HCl-ethyl acetate was added to the purified compound. The reaction mixture was stirred for 30 minutes, and the resulting solid was filtered, and then dried to obtain 3.4g of the object compound (yield: 69%).

Elementary analysis for $C_{22}H_{23}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	53.13	4.66	11.26
Found	52.98	4.71	11.40

Example 40: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylamino-methyl-2,5-dihydropyrrol-1-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.8g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-(N-methyl-t-butoxycarbonyl-amino)methyl-2,5-dihydropyrrol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid imidazolide and 5.66g of ethyl cyanoacetate as starting materials were subjected to the same process as described in Example 39 to obtain 2.80g of the object compound

(yield: 55%).

Elementary analysis for $C_{24}H_{25}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	55.08	4.81	10.70
Found	55.21	4.85	10.66

Example 41: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo-[3.3.0]oct-1,5-en-3-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.4g of 1-cyclopropyl-6-fluoro-8-chloro-7-(7-t-butoxycarbonyl-3,7-diazabicyclo-[3.3.0]oct-1,5-en-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid imidazolide and 5.66ml of ethyl cyanoacetate as starting materials were subjected to the same process as described in Example 39 to obtain 1.62g of the object compound (yield: 31%).

Elementary analysis for $C_{24}H_{23}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	55.29	4.45	10.75
Found	55.31	4.43	10.79

Example 42: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

The compound obtained from the deprotection step of Example 39 was stirred together with 20ml of 5% HCl-MeOH solution at 25°C for 24 hours, and then diethyl ether was added thereto. The resulting solid was filtered, and then dried to obtain 0.47g of the object compound (yield: 11%).

Elementary analysis for $C_{19}H_{19}Cl_2FN_4O_2$

	C(%)	H(%)	N(%)
Calculated	53.66	4.50	13.17
Found	53.72	4.52	13.21

Example 43: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylamino--methyl-2,5-dihydropyrrol-1-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

The intermediate obtained from Example 40 was subjected to the same process as described in Example 42 to obtain 0.9g of the object compound (yield: 20%).

Elementary analysis for $C_{21}H_{21}Cl_2FN_4O_2$

	C(%)	H(%)	N(%)
Calculated	55.89	4.69	12.41
Found	55.99	4.73	12.42

Example 44: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo-[3.3.0]oct-1,5-en-3-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

The compound obtained prior to deprotection in Example 41 was subjected to the same process as described in Example 42 to obtain 0.67 of the object compound (yield: 15%).

Elementary analysis for $C_{21}H_{19}Cl_2FN_4O$

	C(%)	H(%)	N(%)
Calculated	56.14	4.26	12.47
Found	56.30	4.30	12.49

Example 45: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-

yl)-3-(2,2-dicyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.2g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid imidazolide and 3.30g of malononitrile as starting materials were subjected to the same process as described in Example 39 to obtain 2.56g of the object compound (yield: 57%).

Elementary analysis for $C_{20}H_{18}Cl_2FN_5O_2$

	C(%)	H(%)	N(%)
Calculated	53.35	4.03	15.55
Found	53.50	4.11	15.61

Example 46: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylamino-methyl-2,5-dihydropyrrol-1-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid dissolved in a mixture of 20ml of methanol and 10ml of chloroform. 2.29g of di-t-butyldicarbonate was added to this solution, and the reaction mixture was stirred at 50°C for 3 hours. The solvent was distilled off under reduced pressure, and then subjected to the same processes as described in Examples 32 and 33 to obtain 3.12g of the object compound (yield: 62%).

Elementary analysis for $C_{21}H_{24}Cl_2FN_3O_4S$

	C(%)	H(%)	N(%)
Calculated	50.01	4.80	8.33
Found	50.12	4.85	8.31

Example 47: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo-[3.3.0]oct-1,5-en-3-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-

oxoquinoline hydrochloride

3.9g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 46 to obtain 2.61g of the object compound (yield: 52%).

Elementary analysis for $C_{21}H_{22}Cl_2FN_3O_4S$

	C(%)	H(%)	N(%)
Calculated	50.21	4.41	8.36
Found	50.35	4.48	8.32

Example 48: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diacetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 1.08ml of 2,4-pentadione as starting materials were subjected to the same process as described in Example 20 to obtain 2.27g of the object compound (yield: 47%).

Elementary analysis for $C_{22}H_{24}Cl_2FN_3O_4$

	C(%)	H(%)	N(%)
Calculated	54.56	4.99	8.68
Found	54.66	5.04	8.61

Example 49: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.6g of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 9 to obtain 1.94g of the object

compound (yield: 44%).

Elementary analysis for $C_{19}H_{22}ClFN_4O_5$

	C(%)	H(%)	N(%)
Calculated	51.76	5.03	12.71
Found	51.88	5.11	12.80

Example 50: Preparation of 1-cyclopropyl-6-fluoro-8-methyl-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.4g of 1-cyclopropyl-6-fluoro-8-methyl-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 1.74g of the object compound (yield: 41%).

Elementary analysis for $C_{19}H_{22}ClFN_4O_4$

	C(%)	H(%)	N(%)
Calculated	53.71	5.22	13.19
Found	53.88	5.30	13.15

Example 51: Preparation of 1-cyclopropyl-5-methyl-6-fluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

3.6g of 1-cyclopropyl-5-methyl-6-fluoro-7-(3-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 1 to 4 to obtain 1.45g of the object compound (yield: 33%).

Elementary analysis for $C_{20}H_{24}ClFN_4O_4$

	C(%)	H(%)	N(%)
Calculated	54.73	5.51	12.77
Found	54.60	5.61	12.68

Example 52: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-amido-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

5.2g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid imidazolide and 6.55g of malonamide monoethylester as starting materials were subjected to the same process as described in Example 39 to obtain 1.24g of the object compound (yield: 24%).

Elementary analysis for $C_{22}H_{25}Cl_2FN_4O_5$

	C(%)	H(%)	N(%)
Calculated	51.27	4.89	10.87
Found	51.24	4.98	10.79

Example 53: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminomethyl-pyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

4.8g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-t-butoxycarbonylaminomethyl-pyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylicacid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 2.39g of the object compound (yield: 52%).

Elementary analysis for $C_{19}H_{21}Cl_2FN_4O_4$

	C(%)	H(%)	N(%)
Calculated	49.69	4.61	12.20

Found	49.53	4.69	12.13

Example 54: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-N-methyl-3R-t-butoxycarbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid

14.67g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-methylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid was suspended in 300ml of methanol, and 8.07g of di-t-butyldicarbonate was added thereto. The resulting mixture was reacted at room temperature for 6 hours, the solvent was distilled off under reduced pressure, and the solid formed after addition of mixed solvent of some methanol with diethyl ether is filtered, and then dried under reduced pressure to obtain 14.31g of the object compound (yield: 77%).

Elementary analysis for $C_{23}H_{27}ClFN_3O_5$

	C(%)	H(%)	O(%)	N(%)
Calculated	57.56	5.67	16.67	8.76
Found	57.44	5.70	16.77	8.69

Example 55: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-methyl-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-N-methyl-3R-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 6.37g of the object compound (yield: 57%).

Elementary analysis for $C_{25}H_{30}Cl_2FN_3O_6$

	C(%)	H(%)	O(%)	N(%)
Calculated	53.77	5.41	17.19	7.52

Found	53.90	5.50	17.33	7.44

Example 56: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-methyl-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-N-methyl-3S-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 6.70g of the object compound (yield: 60%).

Elementary analysis for $C_{25}H_{30}Cl_2FN_3O_6$

	C(%)	H(%)	O(%)	N(%)
Calculated	53.77	5.41	17.19	7.52
Found	53.91	5.48	17.30	7.40

Example 57: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylamino-pyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-N-methyl-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 6.14g of the object compound (yield: 55%).

Elementary analysis for $C_{25}H_{30}Cl_2FN_3O_6$

	C(%)	H(%)	O(%)	N(%)
Calculated	53.77	5.41	17.19	7.52
Found	53.80	5.51	17.37	7.48

Example 58: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3R-methyl-

aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.51g of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-N-methyl-3R-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 6.87g of the object compound (yield: 62%).

Elementary analysis for $C_{26}H_{33}ClFN_3O_7$

	C(%)	H(%)	O(%)	N(%)
Calculated	56.37	6.00	20.22	7.58
Found	56.50	6.11	20.35	7.49

Example 59: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3S-methyl-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.51g of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-N-methyl-3S-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 6.43g of the object compound (yield: 58%).

Elementary analysis for $C_{26}H_{33}ClFN_3O_7$

	C(%)	H(%)	O(%)	N(%)
Calculated	56.37	6.00	20.22	7.58
Found	56.43	6.09	20.31	7.44

Example 60: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.51g of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-N-methyl-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same process as described in Example 20 to obtain 7.31g of the object compound (yield: 66%).

Elementary analysis for $C_{26}H_{33}ClFN_3O_7$

	C(%)	H(%)	O(%)	N(%)
Calculated	56.37	6.00	20.22	7.58
Found	56.55	6.07	20.30	7.43

Example 61: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-methyl-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-N-methyl-3R-t-butoxycarbonylamino-pyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylicacid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 5.79g of the object compound (yield: 63%).

Elementary analysis for $C_{19}H_{21}Cl_2FN_4O_4$

	C(%)	H(%)	O(%)	N(%)
Calculated	49.69	4.61	13.93	12.20
Found	49.81	4.66	14.09	12.11

Example 62: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-methyl-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-N-methyl-3S-t-butoxy-carbonylaminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to

4 to obtain 5.33g of the object compound (yield: 58%).

Elementary analysis for $C_{19}H_{21}Cl_2FN_4O_4$

	C(%)	H(%)	O(%)	N(%)
Calculated	49.69	4.61	13.93	12.20
Found	49.77	4.66	14.14	12.08

Example 63: Preparation of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylamino-pyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.6g of 1-cyclopropyl-6-fluoro-8-chloro-7-(3-N-methyl-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 5.5g of the object compound (yield: 60%).

Elementary analysis for $C_{19}H_{21}Cl_2FN_4O_4$

	C(%)	H(%)	O(%)	N(%)
Calculated	49.69	4.61	13.93	12.20
Found	49.80	4.70	14.11	12.00

Example 64: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3R-methyl-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.51g of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-N-methyl-3R-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 5.00g of the object compound (yield: 55%).

Elementary analysis for $C_{20}H_{24}ClFN_4O_5$

	C(%)	H(%)	O(%)	N(%)
Calculated	52.81	5.32	17.59	12.32
Found	52.99	5.40	17.68	12.20

Example 65: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3S-methyl-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.51g of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-N-methyl-3S-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 4.64g of the object compound (yield: 51%).

Elementary analysis for $C_{20}H_{24}ClFN_4O_5$

	C(%)	H(%)	O(%)	N(%)
Calculated	52.81	5.32	17.59	12.32
Found	53.03	5.39	17.77	12.19

Example 66: Preparation of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylamino-pyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride

9.51g of 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-N-methyl-t-butoxycarbonyl-aminopyrrolidin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as a starting material was subjected to the same processes as described in Examples 2 to 4 to obtain 5.28g of the object compound (yield: 58%).

Elementary analysis for $C_{20}H_{24}ClFN_4O_5$

	C(%)	H(%)	O(%)	N(%)
Calculated	52.81	5.32	17.59	12.32

Found	52.93	5.44	17.72	12.11

Example 67: Preparation of organic or inorganic acid addition salts.

The compounds prepared in the above Examples were dissolved in water, and then the pH of this solution was adjusted to about 7 to precipitate the solid. The resulting solid was filtered, dried, and then dissolved in a mixture of chloroform-methanol. Various organic acids such as lactic acid, ascorbic acid, maleic acid, malonic acid, glutamic acid, citric acid, fumaric acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, propionic acid, tartaric acid, succinic acid or methanesulfonic acid, or inorganic acids such as sulfuric acid, nitric acid or the like were added to the above solution in the ratio of equivalent, and then the solvent was removed to give various acid addition salts.

The novel quinoline antibiotics of the present invention may be formulated in the form of injection or oral preparation. The examples of these preparations are as follows:

Formulation

Example I

A capsule formulation was prepared in accordance with the following composition:

Component	Amount
Compound prepared in Example 56	100.0mg
Corn starch	25.0mg
Calcium carboxymethyl cellulose	23.0mg
Magnesium stearate	2.0mg
Total	150.0mg

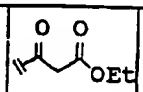
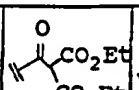
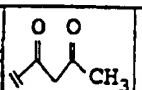
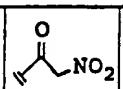
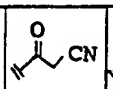
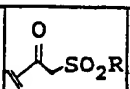
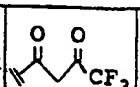
Example II

A solution formulation was prepared in accordance with the following composition:

Component	Amount
Compound prepared in Example 56	1 to 10g
Lactic acid or Sodium hydroxide	0.1 to 2g
Mannitol	0.1g
Deionized water	87.9 to 98.8g
Total	100g

The pKa values of the compounds synthesized in the present invention which were determined by a general manner and the pKa value of a carboxylic acid are shown in Table 1.

Table 1

								
pKa	≃10 ≃8(enol)	≃7	≃8	≃5	≃8	≃10	≃5	≃6

It has been apparent from the above table that the activity of the compounds prepared by converting C-3 carboxy groups of conventional quinolone compounds and the acidity of proton at their active methylene site have a quite close correlation. Furthermore, the acidity of active methylene proton is hardly affected from the size of the adjacent electron withdrawing group.

The antibacterial activities of the compounds, in which 2-nitroacetyl group and the like were substituted, were greatly increased against gram-positive bacteria as compared with the reference carboxylic acid derivative, and maintained at a nearly same level as the carboxylic acid derivative against gram-negative bacteria(see Table2)

The compounds prepared in the Examples were tested as follows:

1. In vitro antibacterial activity test

The antibacterial activities of the compounds prepared by introducing the groups having the above pKa values into the C-3 position are shown in Table 2.

Table 2

In Vitro Anti-Bacterial Activity Test (MIC, μg/ml)

	Example 4	Example 5	Example 6	Example 7	Example 8	Example 9	Example 10	Example 11
Streptococcus pyogenes 308A	3.125	3.125	3.125	1.563	0.781	0.195	1.563	0.195
Streptococcus pyogenes 77A	0.781	0.781	0.781	0.781	0.195	0.195	0.781	0.098
Streptococcus faecium MD8b	0.781	0.781	0.781	0.781	0.391	0.195	1.563	0.098
Staphylococcus aureus SG511	0.195	0.195	0.098	0.391	0.049	0.025	0.391	0.013
Staphylococcus aureus 285	0.391	0.195	0.195	0.391	0.025	0.025	0.391	0.025
Staphylococcus aureus 503	0.781	0.781	0.391	0.391	0.025	0.013	0.391	0.025
Escherichia coli 078	<0.002	<0.002	<0.002	0.049	0.007	0.007	0.049	<0.002
Escherichia coli DC0	0.195	0.195	0.195	0.391	0.195	0.195	1.563	0.049
Escherichia coli DC2	0.391	0.391	0.098	0.391	0.013	0.025	0.391	0.013
Escherichia coli TEM	0.013	0.007	<0.002	0.195	<0.002	<0.002	0.098	<0.002
Escherichia coli 1507E	0.007	0.013	<0.002	0.025	0.007	0.013	0.098	<0.002
Pseudomonas aeruginosa 9027	0.195	0.195	0.391	0.781	0.391	0.391	3.125	0.195
Pseudomonas aeruginosa 1592E	0.195	0.195	0.195	0.781	0.195	0.098	1.563	0.195
Pseudomonas aeruginosa 1771	0.195	0.195	0.195	1.563	0.391	0.195	3.125	0.098
Pseudomonas aeruginosa 1771M	0.098	0.049	0.049	0.391	0.049	0.049	1.563	0.025
Salmonella typhimurium	0.007	0.007	<0.002	0.098	0.007	0.007	0.049	<0.002
Klebsiella oxytoca 1082E	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	0.025	<0.002
Klebsiella aerogenes 1522E	0.013	0.025	0.007	0.391	0.007	0.004	1.563	0.007
Enterobacter cloacae P99	0.007	0.007	<0.002	0.391	<0.002	<0.002	0.049	<0.002
Enterobacter cloacae 1321E	<0.002	<0.002	<0.002	0.013	<0.002	0.007	0.049	<0.002

Table 2 (continued)

	Example 12	Example 13	Example 14	Example 15	Example 16	Example 18	Example 19	Example 20
Streptococcus pyogenes 308A	0.391	0.195	1.563	0.049	0.098	3.125	3.125	0.391
Streptococcus pyogenes 77A	0.195	0.195	0.195	0.025	0.025	0.781	1.563	0.098
Streptococcus faecium MD8b	0.098	0.195	0.391	0.025	0.013	0.781	0.781	0.098
Staphylococcus aureus SG511	0.025	0.025	0.098	<0.002	0.004	0.195	0.391	0.013
Staphylococcus aureus 285	0.025	0.025	0.098	0.004	0.004	0.391	1.563	0.013
Staphylococcus aureus 503	0.025	0.049	0.049	<0.002	<0.002	0.391	0.781	0.025
Escherichia coli 078	<0.002	<0.002	<0.002	<0.002	0.004	0.004	0.004	<0.002
Escherichia coli DC0	0.098	0.049	0.098	0.098	0.098	0.195	0.391	0.098
Escherichia coli DC2	0.049	0.013	0.049	0.013	0.013	0.098	0.391	0.013
Escherichia coli TEM	0.004	<0.002	0.007	0.004	0.004	0.007	0.195	<0.002
Escherichia coli 1507E	0.004	0.004	0.013	0.007	0.013	0.004	0.013	0.007
Pseudomonas aeruginosa 9027	0.391	0.195	0.781	0.781	0.781	0.781	0.781	0.391
Pseudomonas aeruginosa 1592E	0.391	0.195	0.781	0.391	0.781	0.391	1.563	0.195
Pseudomonas aeruginosa 1771	0.195	0.195	0.391	0.391	0.391	0.195	0.781	0.195
Pseudomonas aeruginosa 1771M	0.049	0.049	0.195	0.195	0.195	0.049	1.563	0.098
Salmonella typhimurium	<0.002	<0.002	<0.002	<0.002	<0.02	0.007	0.391	<0.002
Klebsiella oxytoca 1082E	<0.002	<0.002	<0.002	<0.002	0.007	0.004	0.013	<0.002
Klebsiella aerogenes 1522E	0.025	0.013	0.025	0.013	0.013	0.013	0.049	0.025
Enterobacter cloacae P99	0.004	0.004	0.007	0.004	0.007	<0.002	0.013	<0.002
Enterobacter cloacae 1321E	<0.002	<0.002	<0.002	<0.002	0.007	<0.002	0.013	<0.002

Table 2 (continued)

	Example 21	Example 22	Example 23	Example 24	Example 25	Example 26	Example 27	Example 28
Streptococcus pyogenes 308A	0.781	0.391	0.781	0.391	0.781	1.563	0.781	0.098
Streptococcus pyogenes 77A	0.391	0.781	0.195	0.391	0.391	0.781	0.391	0.049
Streptococcus faecium MD8b	0.781	0.391	0.195	0.391	0.391	0.781	0.391	0.049
Staphylococcus aureus SG511	0.049	0.049	0.049	0.049	0.098	0.098	0.098	0.004
Staphylococcus aureus 285	0.049	0.098	0.049	0.049	0.049	0.098	0.049	0.007
Staphylococcus aureus 503	0.049	0.049	0.049	0.049	0.049	0.098	0.049	<0.002
Escherichia coli 078	0.004	0.004	<0.002	<0.002	<0.002	0.004	0.004	<0.002
Escherichia coli DC0	0.098	0.098	0.195	0.098	0.098	0.195	0.098	0.195
Escherichia coli DC2	0.049	0.025	0.049	0.025	0.025	0.098	0.013	0.049
Escherichia coli TEM	0.013	<0.002	0.004	<0.002	<0.002	0.013	<0.002	0.013
Escherichia coli 1507E	0.013	<0.002	0.013	<0.002	0.025	0.025	0.013	0.013
Pseudomonas aeruginosa 9027	0.391	0.781	0.781	0.391	0.391	0.781	0.391	0.781
Pseudomonas aeruginosa 1592E	0.391	0.781	0.391	0.391	0.195	0.781	0.195	0.391
Pseudomonas aeruginosa 1771	0.195	0.781	0.391	0.391	0.195	0.781	0.195	0.781
Pseudomonas aeruginosa 1771M	0.098	0.195	0.098	0.049	0.098	0.098	0.098	0.195
Salmonella typhimurium	0.013	0.004	0.004	<0.002	0.004	0.007	<0.002	0.013
Klebsiella oxytoca 1082E	0.004	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	0.007
Klebsiella aerogenes 1522E	0.025	0.025	0.025	0.013	0.013	0.049	0.013	0.013
Enterobacter cloacae P99	0.007	0.004	0.004	<0.002	0.004	0.013	0.004	<0.002
Enterobacter cloacae 1321E	<0.002	<0.002	<0.002	<0.002	<0.002	0.004	<0.002	<0.002

Table 2 (continued)

	Example 29	Example 30	Example 31	Example 33	Example 34	Example 35	Example 36	Example 37
Streptococcus pyogenes 308A	0.391	1.563	3.125	3.125	0.391	0.195	0.391	1.563
Streptococcus pyogenes 77A	0.098	1.563	1.563	3.125	0.098	0.098	0.098	3.125
Streptococcus faecium MD8b	0.098	1.563	0.781	6.25	0.098	0.098	0.195	3.125
Staphylococcus aureus SG511	0.013	0.195	0.781	1.563	0.025	0.025	0.025	0.781
Staphylococcus aureus 285	0.049	0.195	0.391	1.563	0.049	0.025	0.049	0.781
Staphylococcus aureus 503	0.013	0.195	0.391	0.781	0.098	0.013	0.049	0.781
Escherichia coli 078	0.013	0.049	0.391	0.195	<0.002	0.007	0.007	0.391
Escherichia coli DC0	0.195	0.781	0.195	0.195	0.195	0.098	0.195	0.781
Escherichia coli DC2	0.098	0.195	0.391	0.098	0.098	0.049	0.049	0.391
Escherichia coli TEM	0.013	0.391	0.195	0.098	0.007	0.013	0.025	0.098
Escherichia coli 1507E	0.049	0.391	0.198	0.195	0.007	0.007	0.025	0.195
Pseudomonas aeruginosa 9027	1.563	0.781	0.781	1.563	0.391	0.781	1.563	1.563
Pseudomonas aeruginosa 1592E	0.781	0.781	0.781	1.563	0.391	0.781	0.781	3.125
Pseudomonas aeruginosa 1771	1.563	0.391	0.781	1.563	0.195	0.391	0.781	1.563
Pseudomonas aeruginosa 1771M	0.391	0.195	0.391	0.781	0.098	0.098	0.195	0.781
Salmonella typhimurium	0.391	0.781	0.391	0.781	0.004	0.013	0.025	0.195
Klebsiella oxytoca 1082E	0.049	0.391	0.195	0.391	<0.002	<0.002	0.007	0.195
Klebsiella aerogenes 1522E	0.013	0.098	0.098	0.391	0.013	0.013	0.025	0.391
Enterobacter cloacae P99	0.013	0.049	0.098	0.195	0.007	0.025	0.025	0.195
Enterobacter cloacae 1321E	0.007	0.049	0.049	0.098	0.049	0.025	0.025	0.195

Table 2.(continued)

	Example 38	Example 39	Example 40	Example 41	Example 42	Example 43	Example 44	Example 45
Streptococcus pyogenes 308A	1.563	25	25	25	25	25	25	25
Streptococcus pyogenes 77A	0.781	6.25	12.5	12.5	12.5	25	25	25
Streptococcus faecium MD8h	0.781	6.25	12.5	25	12.5	12.5	25	6.25
Staphylococcus aureus SG511	0.391	1.563	1.563	3.125	6.25	3.125	6.25	0.781
Staphylococcus aureus 285	0.781	1.563	3.125	6.25	3.125	3.125	6.25	1.563
Staphylococcus aureus 503	0.391	1.563	1.563	6.25	3.125	0.195	6.25	1.563
Escherichia coli 078	0.195	0.049	0.098	0.049	0.098	6.25	0.195	0.049
Escherichia coli DC0	0.195	6.25	6.25	3.125	12.5	3.125	3.125	1.563
Escherichia coli DC2	0.098	3.125	3.125	1.563	3.125	1.563	1.563	0.781
Escherichia coli TEM	0.195	0.391	0.391	0.195	0.781	1.563	0.391	0.195
Escherichia coli 1507E	0.098	0.781	0.781	0.391	0.195	12.5	0.781	0.195
Pseudomonas aeruginosa 9027	1.563	12.5	12.5	6.25	2.5	6.25	12.5	6.25
Pseudomonas aeruginosa 1592E	0.781	12.5	6.25	3.125	12.5	12.5	6.25	3.125
Pseudomonas aeruginosa 1771	1.563	12.5	6.25	3.125	6.25	3.125	12.5	3.125
Pseudomonas aeruginosa 1771M	0.391	3.125	3.125	1.563	6.25	1.563	3.125	0.781
Salmonella typhimurium	0.049	0.391	0.195	0.098	1.563	0.195	0.195	0.098
Klebsiella oxytoca 1082E	0.025	0.049	0.049	0.049	0.098	0.098	0.195	0.049
Klebsiella aerogenes 1522E	0.098	0.781	0.391	0.195	1.563	0.781	0.391	0.391
Enterobacter cloacae P99	0.098	0.391	0.391	0.098	0.781	0.391	0.195	0.195
Enterobacter cloacae 1321E	0.049	0.049	0.049	0.049	0.098	0.049	0.098	0.098

Table 2 (continued)

	Example 46	Example 47	Example 48	Example 49	Example 50	Example 51	Example 52	Example 53
Streptococcus pyogenes 308A	1.563	1.563	0.781	0.391	0.781	0.781	0.195	0.098
Streptococcus pyogenes 77A	0.391	0.781	0.391	0.098	0.391	0.391	0.391	0.049
Streptococcus faecium MD8b	0.195	0.781	0.195	0.195	0.195	0.391	0.391	0.049
Staphylococcus aureus SG511	0.098	0.391	0.195	0.098	0.098	0.195	0.025	0.013
Staphylococcus aureus 285	0.049	0.195	0.195	0.098	0.098	0.098	0.025	0.007
Staphylococcus aureus 503	0.049	0.391	0.195	0.098	0.098	0.098	0.025	0.013
Escherichia coli 078	0.025	0.195	0.049	0.049	0.025	0.025	0.007	<0.002
Escherichia coli DC0	0.391	0.781	0.391	0.391	0.195	0.781	0.049	0.195
Escherichia coli DC2	0.098	0.391	0.098	0.098	0.049	0.195	0.025	0.049
Escherichia coli TEM	0.049	0.195	0.049	0.049	0.049	0.049	<0.002	0.013
Escherichia coli 1507E	0.098	0.391	0.195	0.098	0.098	0.049	0.004	0.025
Pseudomonas aeruginosa 9027	1.563	1.563	3.125	3.125	1.563	0.781	0.781	0.781
Pseudomonas aeruginosa 1592E	0.781	0.781	1.563	1.563	0.781	0.391	0.391	0.391
Pseudomonas aeruginosa 1771	1.563	0.781	3.125	3.125	1.563	0.781	0.391	0.781
Pseudomonas aeruginosa 1771M	0.195	0.195	0.781	0.781	0.391	0.195	0.098	0.195
Salmonella typhimurium	0.195	0.098	0.391	0.049	0.013	0.025	0.013	0.013
Klebsiella oxytoca 1082E	0.013	0.098	0.195	0.013	0.013	0.013	<0.002	<0.002
Klebsiella aerogenes 1522E	0.013	0.049	0.195	0.098	0.195	0.195	0.013	0.013
Enterobacter cloacae P99	0.098	0.049	0.098	0.049	0.013	0.025	0.004	0.013
Enterobacter cloacae 1321E	0.049	0.049	0.098	0.025	0.013	0.025	<0.002	<0.002

Table 2 (continued)

	Example 55	Example 56	Example 57	Example 58	Example 59	Example 60
Streptococcus pyogenes 308A	1.563	0.781	0.781	1.563	0.781	1.563
Streptococcus pyogenes 77A	0.391	0.195	0.195	1.563	0.781	0.781
Streptococcus faecium MD8b	0.391	0.195	0.098	1.563	0.781	0.781
Staphylococcus aureus SG511	0.098	0.049	0.049	0.195	0.098	0.195
Staphylococcus aureus 285	0.195	0.098	0.195	0.195	0.098	0.195
Staphylococcus aureus 503	0.195	0.098	0.195	0.195	0.098	0.098
Escherichia coli 078	0.013	0.007	0.007	0.098	0.049	0.098
Escherichia coli DC0	0.391	0.195	0.049	1.563	0.781	0.781
Escherichia coli DC2	0.098	0.049	0.025	0.195	0.098	0.098
Escherichia coli TEM	0.025	0.013	0.013	0.098	0.049	0.098
Escherichia coli 1507E	0.025	0.013	0.013	0.391	0.391	0.195
Pseudomonas aeruginosa 9027	1.563	0.781	1.563	1.563	1.563	1.563
Pseudomonas aeruginosa 1592E	0.391	0.391	0.781	1.563	1.563	1.563
Pseudomonas aeruginosa 1771	0.391	0.391	0.391	1.563	1.563	1.563
Pseudomonas aeruginosa 1771M	0.195	0.098	0.195	0.781	0.781	0.781
Salmonella typhimurium	0.013	0.007	0.013	0.195	0.049	0.098
Klebsiella oxytoca 1082E	0.025	0.013	0.049	0.049	0.007	0.013
Klebsiella aerogenes 1522E	0.049	0.049	0.049	0.195	0.098	0.195
Enterobacter cloacae P99	0.025	0.013	0.013	0.098	0.049	0.098
Enterobacter cloacae 1321E	0.049	0.049	0.049	0.098	0.049	0.098

Table 2 (continued)

	Example 61	Example 62	Example 63	Example 64	Example 65	Example 66
Streptococcus pyogenes 308A	0.391	0.098	0.391	0.781	0.781	1.563
Streptococcus pyogenes 77A	0.098	0.049	0.098	0.781	0.781	0.781
Streptococcus faecium MD8b	0.098	0.049	0.098	0.391	0.781	0.781
Staphylococcus aureus SG511	0.013	0.013	0.025	0.391	0.049	0.391
Staphylococcus aureus 285	0.025	0.025	0.049	0.098	0.049	0.391
Staphylococcus aureus 503	0.025	0.013	0.049	0.098	0.098	0.098
Escherichia coli 078	<0.002	<0.002	<0.002	0.049	0.049	0.098
Escherichia coli DC0	0.049	0.025	0.098	0.391	0.781	0.781
Escherichia coli DC2	0.013	0.013	0.025	0.049	0.195	0.195
Escherichia coli TEM	0.007	0.007	0.007	0.049	0.049	0.195
Escherichia coli 1507E	0.007	0.007	0.007	0.098	0.195	0.391
Pseudomonas aeruginosa 9027	0.195	0.195	0.391	1.563	1.563	1.563
Pseudomonas aeruginosa 1592E	0.195	0.098	0.195	1.563	1.563	1.563
Pseudomonas aeruginosa 1771	0.195	0.098	0.195	0.781	1.563	1.563
Pseudomonas aeruginosa 1771M	0.098	0.098	0.049	0.781	1.563	1.563
Salmonella typhimurium	0.004	0.025	0.004	0.013	0.781	0.781
Klebsiella oxytoca 1082E	0.004	<0.002	0.007	0.007	0.049	0.098
Klebsiella aerogenes 1522E	0.013	0.007	0.013	0.098	0.049	0.013
Enterobacter cloacae P99	0.007	0.007	0.013	0.049	0.013	0.195
Enterobacter cloacae 1321E	0.007	0.007	0.013	0.049	0.013	0.049

Table 2 (continued)

	ciprofloxacin
Streptococcus pyogenes 308A	3.125
Streptococcus pyogenes 77A	0.781
Streptococcus faecium MD8b	0.781
Staphylococcus aureus SG511	0.195
Staphylococcus aureus 285	0.391
Staphylococcus aureus 503	0.781
Escherichia coli 078	<0.002
Escherichia coli DC0	0.195
Escherichia coli DC2	0.098
Escherichia coli TEM	0.004
Escherichia coli 1507E	0.004
Pseudomonas aeruginosa 9027	0.391
Pseudomonas aeruginosa 1592E	0.195
Pseudomonas aeruginosa 1771	0.195
Pseudomonas aeruginosa 1771M	0.049
Salmonella typhimurium	0.004
Klebsiella oxytoca 1082E	<0.002
Klebsiella aerogenes 1522E	0.013
Enterobacter cloacae P99	<0,002
Enterobacter cloacae 1321E	<0,002

The above in vitro antibacterial activity test was carried out in accordance with the agar culture medium dilution method (Hoechst 345) by using Muller-Hinton agar medium to determine the minimum inhibitory concentration (MIC).

The strains having 10^7 C.F.U./ml were inoculated on the culture medium, and the growth of the strains was observed after incubating them at 37°C for 18 hours, in which ciprofloxacin was used as a control antibacterial agent. In this test, twenty typical strains were used.

Thus, the present invention provides a novel quinoline-antibacterial agents having the new formula as well as an excellent solubility and antibacterial activity as compared with the known antibiotics by introducing a new ketone derivative including acidic proton other than a carboxy group into the C-3 position.

2. Treatment effect on the systemic infection

10 fold of the pathogens which lead to 100% lethality were injected intraperitoneally to male and female NMRI mice weighing 18 to 20g. Immediately and 4 hours after injection, the dose of test compounds, which was determined by two-fold serial dilution method, was administered orally or subcutaneously to the mice, and on the 10th day, the effect was evaluated in terms of ED_{50} calculated from the number of survived mice by the probit analysis. The results of the test are shown in Table 3.

Table 3

Treatment Effect on the Systemic Infection

Pathogens	Compound	ED_{50}:mg/kg	
		Subcutaneous Injection	Oral Administration
S.aureus 17740	Example 13	16.8	127.7
	Example 16	97.6	49.7
	Ofloxacin	200.0	>200.0
	Ciprofloxacin	132.3	>200.0
P.mirabilis	Example 13	0.08	0.21
	Example 34	0.16	0.41
	Ofloxacin	0.33	1.64
	Ciprofloxacin	0.16	0.82

3. Acute Toxicity Test

Test compounds were administered to ICR mice weighing 20 to 25g. On 14th day, LD_{50} was calculated from the number of survived mice by the probit analysis. The results of the test are shown in Table 4.

Table 4

Acute Toxicity Test

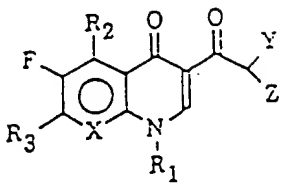
Compound	Acute Toxicity (LD_{50}:mg/kg)	
	Peritomeo Injection	Oral Administration
Example 13	580	3800
Example 16	605	3800
Example 34	620	4000

As can be seen from the above results, the compounds of the present invention possess a broad spectrum of potent antibacterial activity against gram-positive and gram-negative bacteria as compared with the known quinolone antibiotics, ciprofloxacin and ofloxacin. The compounds of the present invention also exhibit an excellent activity as compared with the known quinolone antibiotics in terms of 50% effective dose (ED_{50}) on the systemic bacterial infection. Further, it has been proved that the compounds of the present invention have a low toxicity sufficient to be useful as drugs as a result of the acute toxicity test and no effects on the cardiovascular system of the dogs, particularly blood pressure lowering effect.

Accordingly, the compounds of the present invention may be advantageously used as therapeutically active compounds and preservatives of inorganic and organic materials.

What is claimed is:

1. A quinoline derivative of formula (I):



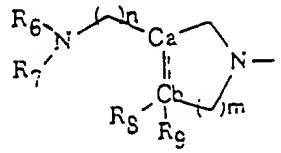
(I)

wherein:

R_1 is a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms, a straight chain or cyclic lower alkyl group having 1 to 3 carbon atoms which is substituted with a halogen atom, a phenyl group or a phenyl group substituted with one or two halogen atoms;

R_2 is a hydrogen atom, a lower alkyl or amino group;

R_3 is a halogen atom or a substituted or unsubstituted heterocyclic group represented by the following formula (A) which contains at least one nitrogen atom as a hetero atom in the ring;



(A)

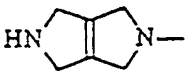
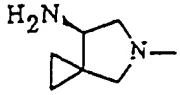
wherein:

R_6, R_7, R_8 and R_9 are each hydrogen atoms or lower alkyl groups, or two of these groups may form a bond, m and n are 0 or 1, and C_a-C_b may not form a bond, or is a single or double bond;

X is nitrogen atom or C-R_4 wherein R_4 is hydrogen or halogen atom, or lower alkyl or lower alkoxy group; and

Y and Z are each hydrogen atoms, or electron withdrawing groups, for example, ester, cyano, nitro, acyl or substituted acyl, substituted or unsubstituted amide group, lower alkylsulfoxy or lower alkylsulfonyl group, and pharmaceutically acceptable acid addition salts thereof.

2. The compound of Claim 1, wherein R_1 is ethyl, cyclopropyl, 2-fluoroethyl or 2,4-difluorophenyl group; and R_3 is substituted or unsubstituted piperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, 3-aminomethyl-2,5-dihydropyrrole,

 or  group.

3. The compound of Claim 1, wherein the compound of formula (I) is one of the following compounds:

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline trifluoroacetate;

1-cyclopropyl-6,8-difluoro-7-(piperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-(2,4-difluorophenyl)-6-fluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxo-1,8-naphthyridine hydrochloride;

1-(2,4-difluorophenyl)-6-fluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-

dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-5-amino-6,8-difluoro-7-(3,5-cis-dimethylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylaminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-aminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-aminopyrrolidin-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-ethyl-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3S-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-3R-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylaminopyrrolidin-1-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-(2-fluoroethyl)-6,8-difluoro-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(7-amino-5-azaspiro[2.4]hept-5-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2,2-diethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-acetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-trifluoroacetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-cyano-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-cyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-dicyanoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-methylaminomethyl-2,5-dihydropyrrol-1-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3,7-diazabicyclo[3.3.0]oct-1,5-en-3-yl)-3-(2-methanesulfonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2,2-diacetoacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-methoxy-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

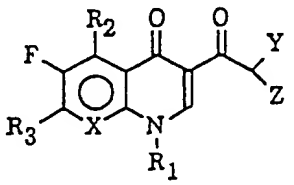
1-cyclopropyl-6-fluoro-8-methyl-7-(3-aminopyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-5-methyl-6-fluoro-7-(3-methylpiperazin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride;

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminopyrrolidin-1-yl)-3-(2-amido-2-ethoxycarbonylacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride; and

1-cyclopropyl-6-fluoro-8-chloro-7-(3-aminomethylpyrrolidin-1-yl)-3-(2-nitroacetyl)-1,4-dihydro-4-oxoquinoline hydrochloride.

4. An antibacterial composition comprising a compound of formula (I) or its acid addition salt as an active ingredient and pharmaceutically acceptable excipients.

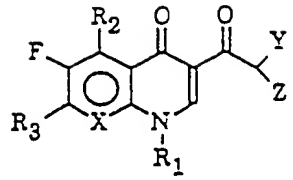


(I)

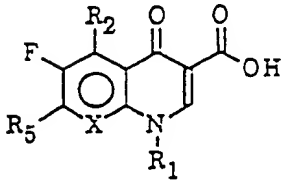
wherein:

R_1, R_2, R_3, X, Y and Z are the same as defined in Claim 1.

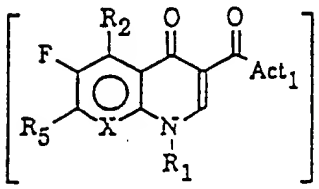
5. A process for preparing quinoline derivatives of formula (I) and pharmaceutically acceptable acid addition salts thereof which comprises activating a carboxy group of the quinoline compound of the following formula (II) with a carboxylic acid activating reagent to give a compound of the following formula (III), reacting the compound of formula (III) with an alkali or alkaline earth metal salt of a compound having an activated methylene group of formula, Y-CH_2-Z to give a compound of the following formula (IV), and finally deprotecting the compound of formula (IV):



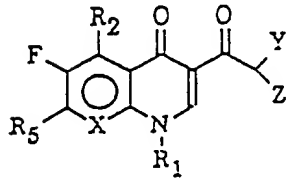
(I)



(II)



(III)



(IV)

wherein:

R_1, R_2, R_3, X, Y and Z are the same as defined in Claim 1;

R_5 is R_3 having protected amino group; and

Act_1 is -CN, substituted or unsubstituted phenoxy group, imidazole or carbonic acid ester group, or mixed anhydride with activated ester organic acid.

6. The process of Claim 5, wherein said carboxylic acid activating reagent is selected from the group consisting of alkoxychloroformates, carbonyldiimidazoles, organic acid anhydrides, carbonates and phosphonates.

7. The process of Claim 5, wherein said alkali or alkaline earth metal ion is Na^+, K^+ or Mg^{2+}.

8. The process of Claim 5, wherein said deprotection reaction is carried out in a 1-10% HCl-methanol solution, CF_3CO_2H or a 1-10% HCl-ethylacetate solution at a temperature between 0° and 80°C.

9. The process of Claim 5, wherein said acid addition salts of the compound of formula (I) are prepared by dissolving hydrochloride or trifluoroacetate of said compound in water while the pH of the solution is adjusted to about 7, filtering and drying the resulting solid, dissolving the dried solid in a lower alkanol, haloalkane or a mixture thereof, and then adding pharmaceutically acceptable organic or inorganic acids thereto.

10. The process of Claim 9, wherein said lower alkanol is methanol or ethanol, and said haloalkane is chloroform, dichloromethane or 1,2-dichloroethane.

11. The process of Claim 9, wherein said organic acid is selected from the group consisting of lactic acid, ascorbic acid, maleic acid, malonic acid, glutamic acid, citric acid, fumaric acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, propionic acid, tartaric acid, succinic acid and methanesulfonic acid, and said inorganic acid is selected from the group consisting of hydrochloric acid, sulfuric acid and nitric acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 93/00044

A. CLASSIFICATION OF SUBJECT MATTER

IPC[5]: C 07 D 401/04, 471/04, 487/04; A 61 K 31/47, 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[5]: C 07 D 401/04, 471/04, 487/04; A 61 K 31/47, 31/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chemical Abstracts (Columbus, Ohio, USA), AT

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel/DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, vol. 95, no. 13, issued 1981 September 28 (Columbus, Ohio, USA), Dainippon Pharmaceutical Co. Ltd. "6-Fluoro-1,8-naphthyridin derivatives" page 713, column 2, the abstract no. 115 597d, JP,A1, 81-45 473.	1,2,4,5
A		3,6-11
X	Chemical abstracts, vol. 113, no. 23, issued 1990 December 3 (Columbus, Ohio, USA), D. Coto "Preparation of ciprofloxacin", page 772, column 2, the abstract no. 212 017n, ES,A1,2 012 307.	1,2
A		3-11
X	Chemical Abstracts, vol. 106, no. 3, issued 1987, January 19 (Columbus, Ohio, USA), C. Dotti "Procedure for obtaining norfloxacin", page 614, column 2, the abstract no. 18 619a, ES,A1,539 111.	1,2
A		3-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
02 August 1993 (02.08.93)	16 August 1993 (16.08.93)

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Form PCT/ISA/210 (second sheet) (July 1992)